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Non-coding RNAs in *Saccharomyces cerevisiae*: what is the function?

Jian Wu, Daniela Delneri and Raymond T. O'Keefe[1]
Faculty of Life Sciences, University of Manchester, Michael Smith Building, Oxford Road, Manchester M13 9PT, U.K.

Abstract

New sequencing technologies and high-resolution microarray analysis have revealed genome-wide pervasive transcription in many eukaryotes, generating a large number of RNAs with no coding capacity. The focus of current debate is whether many of these ncRNAs (non-coding RNAs) are functional, and if so, what their function is. In this review, we describe recent discoveries in the field of ncRNAs in the yeast *Saccharomyces cerevisiae*. Newly identified ncRNAs in this budding yeast, their functions in gene regulation and possible mechanisms of action are discussed.

The development of new technologies, including high-resolution tiling arrays and second-generation sequencing (e.g. RNA-Seq), has revealed that a large fraction of the eukaryotic genome is transcribed, even in areas previously thought to be transcriptionally inactive, such as non-coding regions [1,2]. While providing us with novel information about genome-wide occupancy of the transcriptional machinery, these observations also raise a major question as to whether the RNAs transcribed from these regions have any biological functions or are they just transcriptional noise that is ultimately degraded by the RNA surveillance pathways. Recent studies from a variety of eukaryotic organisms from yeast to humans have demonstrated that at least transcription of a subset of ncRNAs (non-coding RNAs), especially those nearby protein-coding genes, play a role in transcription regulation [3–5]. The aim of this review is to provide a recent snapshot in the field of ncRNAs in the first sequenced eukaryote *Saccharomyces cerevisiae*. We will focus here on newly identified ncRNAs in this budding yeast, their functions in gene regulation and possible mechanisms of action.

ncRNAs identified in budding yeast

In an early genome-wide transcriptome study, Wyers et al. [6] revealed that a number of transcripts encoded in intergenic regions accumulated in a mutant lacking Rrp6, a catalytic subunit of the nuclear exosome. In contrast, there was little change in expression in the vast majority of ORF (open reading frame)-containing transcripts between wild-type and the *rrp6*Δ mutant. These newly identified non-coding transcripts were transcribed by RNAPII (RNA polymerase II), capped and polyadenylated. More importantly, they were targets of the nuclear exosome and rapidly degraded in wild-type cells. Hence, these transcripts were named CUTs (cryptic unstable transcripts).

More recently, by using newly developed high-resolution tiling arrays and deep sequencing (RNA-seq) techniques, the first high-resolution genomic map of CUTs in *S. cerevisiae* was constructed (http://steinmetzlab.embl.de/NFRsharing/) [7–9]. In addition to ORFs, snoRNAs (small nucleolar RNA) and tRNAs, CUTs account for approximately one-eighth of total transcripts identified by the tiling microarray approach. Furthermore, a new set of transcripts that are expressed with low abundance in wild-type vegetatively growing yeast cells and do not have any previously annotated features were also identified by the Steinmetz laboratory [7–9]. This class of transcripts were appropriately named SUTs (stable unannotated transcripts), representing approximately 12 % of transcripts revealed by the tiling array analysis. These studies provide further evidence of widespread transcription in *S. cerevisiae*.

In addition to non-coding transcripts being degraded by the nuclear RNA decay pathway, mainly through the exosome, a group of more than 1600 non-coding transcripts were found to be targeted by the cytoplasmic 5′–3′ RNA degradation pathway catalysed by the RNA exonuclease Xrn1 [10,11]. This class of transcripts, in which more than half are antisense to ORFs, were named XUTs (Xrn1-sensitive unstable transcripts). Interestingly, approximately 75 % of SUTs expressed in yeast grown in YPD medium [1 % (w/v) yeast extract/2 % (w/v) peptone/2 % (w/v) glucose] were found to accumulate in the *xrn1*Δ mutant, indicating that they are substrates of Xrn1. This result also suggests that non-coding transcripts are rapidly degraded by either the nuclear or cytoplasmic RNA decay pathways, although little is known about the functional relevance of degradation by one or the other pathway.

Non-coding transcripts are not only revealed during vegetative growth; a novel class of transcripts that accumulated following meiotic development in *S. cerevisiae*

Key words: histone deacetylase (HDAC), non-coding RNA, open reading frame, pervasive transcription, *Saccharomyces cerevisiae*.

Abbreviations used: CD-CUT, cytoplasmically degraded cryptic unstable transcript; HDAC, histone deacetylase; H3K4me2, dimethylation of histone 3 at Lys^4; H3K36me3, trimethylation of histone 3 at Lys^{36}; MUT, meiotic unannotated transcript; ncRNA, non-coding RNA; NFR, nucleosome-free region; ORF, open reading frame; RNAi, RNA interference; RNAPII, RNA polymerase II; SUT, stable unannotated transcript; TERRA, telomeric repeat-associated cryptic ncRNA.

[1]To whom correspondence should be addressed (email rokeefe@manchester.ac.uk).

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were discovered and named MUTs (meiotic unannotated transcripts) [12]. Most of the MUTs are targets of the exosome component Rrp6 during mitotic growth, indicating that they may be a subclass of CUTs. More importantly, some MUTs were transcribed on the antisense strand, and their accumulation is inversely associated with that of a coding gene, suggesting their roles in the sense gene's regulation during meiosis [12]. However, a large number of MUTs were found transcribed in regions with no recognized features, and further study is needed to clarify their function.

Pervasive transcription has also been found in telomeric regions. Yeast TERRAs (telomeric repeat-associated cryptic ncRNAs) are degraded by the nuclear 5′-end RNA decay pathway catalysed by the exonuclease Rat1 [13]. Their stabilization leads to inhibition of telomerase and defects in telomerase-mediated telomere elongation, hence TERRAs are responsible for controlling telomere length [13]. In a more recent study, a group of cryptic transcripts located upstream of many subtelomeric genes, including those involved in metal homoeostasis, were revealed following inactivation of the cytoplasmic NMD (nonsense-mediated mRNA decay) pathway, through mutations in Ubf1 and Xrn1. These non-coding RNAs were named CD-CUTs (cytoplasmically degraded-CUTs) [14]. Transcription of these CD-CUTs was demonstrated to repress the *bona fide* promoters under repressive conditions, by interfering with the binding of RNAPII and transcriptional activators.

Taken together, recent studies have revealed that up to 85 % of the yeast genome is transcribed, including an abundant number of RNAs with no coding capacity [2]. One important characteristic of these newly discovered ncRNAs is that many of them share sequences with previously annotated features, raising the question as to the origins of their transcription.

The strong association of nucleosome positioning with non-coding transcription

It has been reported that about two-thirds of unannotated ncRNA transcription is strongly associated with 5′-NFRs (5′-nucleosome free regions) which allow the binding of RNA polymerase to DNA [9,15]. Transcription from 5′-NFR can generate sense-orientated transcripts on the same strand as the mRNA and antisense-orientated transcripts with respect to the gene. The sense transcription results in partial overlapping transcripts, as exampled by CD-CUTs. The antisense transcription produces divergent transcript pairs which have been shown to be co-ordinately regulated, indicating that they are generated from a bi-directional promoter [8,9]. In fact, a high percentage of eukaryotic transcription is bi-directional [3], raising the question about how the balance is shifted towards the bulk transcription of coding regions. Nucleosomes around promoter regions are substrates for histone modifications and the chromatin remodelling complex [16]. A recent study has demonstrated that the Rpd3 HDAC (histone deacetylase) enforces directionality of bi-directional promoters by deacetylation of promoter proximal nucleosomes, thus preventing activation of antisense transcription [17].

NFRs have also been revealed in the 3′-end of genes in *S. cerevisiae*, facilitating the generation of non-coding transcripts mainly antisense to ORFs. This suggests that hidden antisense promoters exist in terminator proximal regions [9,18]. In support of this hypothesis, cryptic antisense ncRNAs originating from 3′-NFRs were detected in exosome inactive cells lacking the chromatin remodelling complex factor Isw2, which represses the activation of cryptic promoters. In these cells, nucleosomes were repositioned away from the 3′ intergenic region, allowing transcription initiation from cryptic sites. Interestingly, Isw2 has also been shown to be required for repressing ncRNA transcription from 5′-NFRs [18,19], suggesting a general role for Isw2 in repressing ncRNA transcription. Nonetheless, it has been revealed that about one-third of unannotated transcripts in *S. cerevisiae* originate from 3′-NFR [9].

In addition to 5′ and 3′ regions of ORFs, NFRs have also been characterized in intergenic and repetitive non-coding areas. Following the discovery of RNAPII-driven TERRA transcripts, it was revealed that nucleosomes from telomeric regions were displaced by Rap1 [20], indicating that these TERRAs also initiate from NFRs. In another study, it has been reported that loss of RNAPII by heavy RNAPI transcription leads to nucleosome eviction and nucleosome sliding away from NFRs, which may explain the transcription of cryptic ncRNA within the transcribed ribosomal DNA regions [21].

Pervasive transcription: transcriptional noise?

The recent discovery of widespread transcription in *S. cerevisiae* and other eukaryotic genomes has lead to the question about the role of this pervasive transcription. Currently there are mainly three views: the first is that it is just transcriptional noise as a result of depletion of nucleosomes [3]. The second regards it as only 'test and error' by the RNA transcriptional machinery before the proper protein-coding transcription. The third group think at least some of the ncRNAs generated from widespread transcription might play a role in regulating genome plasticity based on the following evidence.

The first example of non-coding transcriptional interference in yeast was provided by the transcription of the sense-orientated ncRNA SRG1 (Figure 1A). The *SRG1* transcript was shown to repress the promoter of the downstream *SER3* gene by blocking the binding of transcription factors when serine is abundant [22]. Recently, it was further revealed that the transcription of *SRG1* positioned a high level of nucleosomes over the *SER3* promoter, which was transcriptional elongation factors Spt6/Spt16-dependent. Because nucleosomes are the main obstacles for transcription, the transcription of *SRG1* prevented transcription factor access to the *SER3* promoter [23]. Similar interference of downstream protein-coding genes by transcription of

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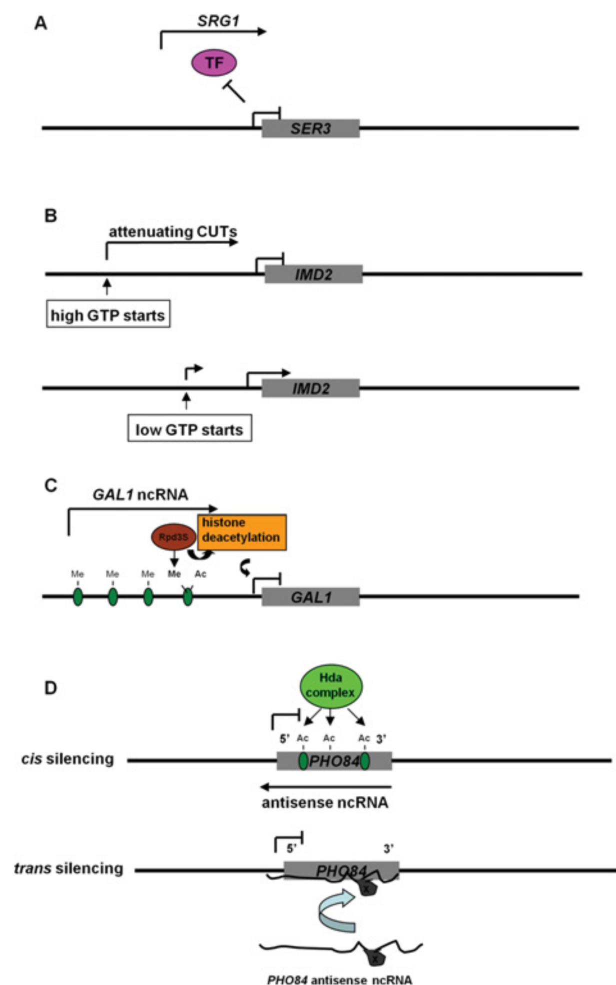
Figure 1 | Possible mechanisms of ncRNA regulation of gene expression in *S. cerevisiae*

(**A**) Transcription of ncRNA *SRG1* represses the downstream *SER3* gene by preventing the binding of transcription factors to the *SER3* promoter. (**B**) Selection of alternative transcription start sites under high GTP or low GTP conditions generates attenuating non-coding CUTs or *IMD2* mRNA respectively. (**C**) Transcription of *GAL1* ncRNA results in high levels of H3K36me3 and H3K4me2/H3K4me3, and elevated histone deacetylation over the *GAL10–GAL1* gene cluster. (**D**) *PHO84* antisense ncRNAs mediate gene silencing *in cis* and *in trans*. *In cis*, the stabilization of *PHO84* antisense CUTs can trigger gene silencing by inducing histone deacetylation through the recruitment of Hda HDAC. *In trans*, *PHO84* antisense RNAs silence *PHO84* by sequence complementary. X, an unidentified potential silencing factor recruited to *PHO84* ncRNA to enhance its silencing activity.



sense-orientated ncRNAs under repressive conditions (e.g. in conditions of metal repletion) has also been observed in other genomic locations, such as subtelomeric regions [14].

In another study, the attenuated regulation of sense-orientated non-coding CUTs on downstream *IMD2* expression was revealed by a different mechanism [24] (Figure 1B). In this case, the selection of alternative transcription start sites within the same promoter generates CUTs or *IMD2* mRNA under repressive (high GTP) or active (low GTP) conditions respectively. It was proposed that transcription of CUTs competed for the available RNAPII pre-initiation complex, resulting in negative regulation of the *IMD2* gene. A similar mechanism was described for the *URA2* loci [25].

Cryptic transcripts located upstream of genes can also affect gene expression by inducing inhibitory chromatin modifications (Figure 1C). Studies regarding the *GAL10–GAL1* gene cluster discovered that cryptic transcripts initiating upstream of *GAL1* in the presence of glucose were responsible for attenuating *GAL1* induction, by depositing the H3K36me3 (trimethylation of histone 3 at Lys^{36}) through Set2 and H3K4me2 (dimethylation of histone 3 at Lys^{4})/H3K4me3 through Set1 [26,27]. These events trigger the binding of Rpd3S HDAC and subsequent histone deacetylation, leading to repression of *GAL1* induction.

Given that a number of SUTs/CUTs are transcribed in the same orientation as the nearby downstream mRNAs [8,9,14], it is possible that regulation mechanisms, such as transcriptional interference, selection of transcriptional start site, epigenetic state of chromatin or other novel mechanism(s) could be revealed in the near future at different gene loci across the yeast genome.

In addition to the sense-orientated ncRNAs, a high proportion of SUTs/CUTs are transcribed in the antisense orientation with respect to protein-coding genes. Uhler et al. [28] identified an antisense CUT originating from the 3′-end of the *PHO5* gene. This CUT was shown to activate, rather than to repress, *PHO5* transcription during phosphate starvation, by enabling histone eviction from the *PHO5* promoter and subsequent RNAPII recruitment. However, this is a rare example of positive gene regulation through an antisense transcript, since a majority of antisense transcripts are generally involved in the anti-regulation of their sense strand [8,9,12].

A well-documented example of antisense ncRNA negatively influencing its counterpart mRNA transcription in *S. cerevisiae* is *PHO84*, which encodes the high-affinity inorganic phosphate transporter (Figure 1D). It was reported that in cells without Rrp6, the stabilization of *PHO84* antisense CUTs induced histone deacetylation via the recruitment of Hda1/2/3 HDAC to *PHO84*, resulting in repression of *PHO84* transcription [29]. Nevertheless, in another study from the same laboratory, it was further revealed that the *PHO84* antisense transcripts mediated *PHO84* gene silencing not only *in cis*, but also *in trans* (Figure 1D). In the latter case, antisense RNAs induced by the Set1 histone methyltransferase, executed gene silencing by sequence complementary to *PHO84*, which was histone deacetylation-independent [30].

In addition to *PHO84*, other examples of antisense transcripts affecting gene expression in *S. cerevisiae* have also been discovered. A cryptic antisense ncRNA initiating from within the TY1 transposon, and sensitive to the cytoplasmic 5′–3′-end degradation pathway catalysed by Xrn1, was reported to be responsible for repression of TY1 expression, which involves Set1 and the associated H3K4me2/H3K4me3

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Table 1 | **Recently identified non-coding RNAs in *S. cerevisiae***

ncRNAs	Biological role	Regulation	Reference(s)
CUTs	Transcriptional regulation?	Rrp6	[8,9]
SUTs	Transcriptional regulation?	Xrn1?	[9]
MUTs	Sense gene regulation during meiosis via mechanisms including antisense or promoter interruption repression	Rrp6	[12]
XUTs	Gene silencing via Set1-dependent histone methylation	Xrn1/lithium toxicity	[11]
CD-CUTs	Repression of subtelomeric genes (e.g. metal homoeostasis genes)	Effectors of nonsense-mediated mRNA decay	[14]
TERRAs	Controlling telomere length via inhibiting telomerase function	Rat1	[13]

[31]. In another case concerning the well-studied PHO (inorganic phosphate) system, the transcription of antisense transcripts has been shown to down-regulate Kcs1p activity, by acting *in trans* by forming hybrids with the *KCS1* mRNA. This leads to subsequent inhibition of *KCS1* mRNA translation [32].

Hence, transcription repression by antisense-orientated ncRNA in sense–antisense transcript pairs is mainly through generation of repressive chromatin modifications on the mRNA region, or through RNAi (RNA interference)-like sequence complementarity as described in higher eukaryotes. However, the components of the RNAi pathway that cleave long double-stranded RNAs into siRNAs (short interfering RNAs) are missing in *S. cerevisiae*.

Conclusions and future directions

It has been widely recognized that widespread transcription is a common feature in yeast and higher eukaryotic genomes [33–35]. The gate towards discovering the mechanisms by which ncRNAs influence protein-coding gene expression is opening (Table 1). However, it is not clear what the precise roles of pervasive transcripts are in regulating gene expression and genome plasticity on a genome wide scale, especially for the large number of nascent transcripts found in regions with previously unannotated features. Moreover, some of the newly identified non-coding RNAs may act as functioning RNAs on their own. These questions could be addressed using different experimental approaches, including a combination of traditional genetic manipulations and more recently developed second-generation RNA sequencing. Once again, the simple eukaryote, the baker's and brewer's yeast *S. cerevisiae*, may provide important clues to better understand how this newly discovered layer of the eukaryotic genome contributes to eukaryotic cell function.

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